THE PREVALENCE OF FUNCTIONAL DYSPEPSIA USING ROME III QUESTIONNAIRE AMONG ADULT PATIENTS ATTENDING KLINIK RAWATAN KELUARGA, HOSPITAL UNIVERSITI SAINS MALAYSIA

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Dissertation Submitted In Partial Fulfillment of The Requirement For The Degree of Master of Medicine (Family Medicine)

UNIVERSITI SAINS MALAYSIA
NOVEMBER 2011

ACKNOWLEDGEMENT

I would like to express my sincere appreciation to the following individuals who have lent their hand in the preparation and completion of this dissertation. My deepest gratitude to my supervisor Dr Juwita Shaaban for her valuable advise and guidance for the preparation of this dissertation. My special thanks to Dr Lee Yeong Yeh from Gastroenterology Unit, Department of Internal Medicine who has given me ideas and has helped me in proposal preparation. My thanks also go to my co supervisors Dr Nazri Mustaffa and also Dr Norwati Daud and not to forget Dr Noorhayati Mohd Noor, a statistician from the Department of Family Medicine for their help. My appreciation also goes to all participants and staff at Klinik Rawatan Keluarga and Klinik Kesihatan Pasir Mas who participated for the sake of knowledge advancement. Finally to my family; my beloved husband Rosli Hamid, my parents Wahab Mat Amin and Ramlah Othman as well as my children Nur Amni Batrisyia, Adam Arief Irfan, Nur Adriana Batrisyia and Nur Anis Batrisyia for their endless love, support, tolerance, patience and encouragement.

Dr Noriza Wahab

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ABBREVIATIONS

BMI	Body Mass Indexed
CI	Confidence Interval
EPS	Epigastric Pain Syndrome
FD	Functional Dyspepsia
FGID	Functional Gastrointestinal Diseases
GERD	Gastroeosophageal Reflux Disease
GI	Gastrointestinal
HRQoL	Health Related Quality of Life
IBS	Irritable Bowel Syndrome
IHD	Ischaemic Heart Disease
OR	Odds Ratio
PDS	Postprandial Distress Syndrome
RM	Ringgit Malaysia
SD	Standard Deviation
UD	Uninvestigated Dyspepsia

ABSTRAK

Prevalen Functional Dyspepsia dikalangan pesakit dewasa Klinik Rawatan Keluarga dengan menggunakan kriteria Rome III.

Pengenalan:

Functional Dyspepsia adalah salah satu penyakit *Functional Gastrointestinal* dimana tiada penyebab- penyebab organik dan pathologi dapat dikenal pasti. Prevalen penyakit ini agak sukar ditentukan kerana ianya memerlukan pemeriksaan endoskopi dan juga terdapat perbezaan kriteria yang digunakan didalam kajian yang lalu.

Objektif:

Tujuan kajian ini dijalankan adalah untuk menetukan prevalen *Functional Dyspepsia* dan faktor-faktor yang berkaitan dengannya.

Metodologi:

Kajian keratan rentas ini telah dijalankan di Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia. Tempoh kajian bermula dari 1 Desember 2009 sehingga 31 Mac 2010. Borang soal selidik Rom III dalam versi Bahasa Malaysia digunakan didalam kajian. Pemeriksaan endoskopi dijalankan bagi memastikan dyspepsia tersebut tidak disebabkan oleh faktor-faktor organik yang lain.

Keputusan:

Sejumlah 192 orang pesakit direkrut di dalam kajian ini dan seramai 32 orang yang tidak melengkapi borang soal selidik dan enggan untuk meneruskan pemeriksaan endoskopi telah disingkirkan daripada kajian. Jumlah yang tinggal adalah seramai 160 orang pesakit. Prevalen *Functional Dyspepsia* adalah 10% (n=16). Sebanyak 68% (n= 11) daripada

mereka yang mendapat *Functional Dyspep*sia menghidap Sindrom *Epigastric Pain* dan sebanyak 32% (n=5) lagi menghidap gabungan Sindrom *Postprandial Distress*. Fakto-faktor yang berkaitan dengan Functional Dyspepsia di dalam analisis univariat adalah berat badan berlebihan (BMI 28 vs 25) kg/m², berkahwin ($p<0.05$) dan mempunyai symptom psikososial ($p<0.05$). Sementara itu analisis multivariat pula telah menunjukkan bahawa mempunyai simptom-simptom Psikososial (OR 3.76,95%CI (1.01-13.99)) dan berkahwin (OR 8.08,95% CI (1.03-63.51)) berkait rapat dengan *Functional Dyspepsia*.

Kesimpulan:

Kajian ini menyokong kajian yang terdahulu yang mendapati bahawa simptom Psikososial berkait dengan *Functional Dyspepsia*. Oleh kerana kebanyakan pesakit - pesakit yang menghidap *Functional Dyspepsia* terdiri daripada mereka yang berkahwin, ini telah menyebabkan terdapat hubungan yang signifikan diantara taraf perkahwinan dan *Functional Dyspepsia.*

ABSTRACT

The Prevalence of Functional Dyspepsia using Rome III Questionnaire among adult patients attending Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia

Introduction:

Functional Dyspepsia is one of the Functional Gastro Intestinal Disease in which there is no specific organic and pathological cause can be identified. It's prevalence is sparse as it requires an endoscopic examination and also due to the different criteria used in different studies.

Objectives:

The aims of this study were to determine the prevalence of functional dyspepsia (FD) and its associated factors

Methodology*:*

This cross sectional study was conducted at Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia. The study period started on 1st December 2009 till 31st March 2010. Self administered Bahasa Malaysia version of Rome III questionnaire was used . Endoscopic examination was performed in order to exclude the organic cause of dyspepsia among patients who fulfill the criteria for Functional Dyspepsia. The diagnosis of Functional Dyspepsia was made based on the normal endoscopic finding.

Results:

A total of 192 patients were recruited and 32 who did not complete the questionnaires and refused endoscopy were excluded. Out of 160 patients, the prevalence of FD was 10% (n= 16). About 68% of the Functional Dyspepsia patients (n= 11) had Epigastric Pain Syndrome

(EPS) and 32% of them (n=5) were those who had mix symptoms of Post prandial Distress Syndrome and EPS. There were significant association between overweight (BMI 28 vs 25 kg/m^2, $p<0.05$), being married ($p<0.05$) and also having psychosocial symptoms ($p< 0.05$) with Functional Dyspepsia in univariate analysis. Multivariate analysis showed psychosocial symptoms (OR 3.76, 95%CI (1.01- 13.99)) and currently married (OR 8.08,95%CI (1.03-63.51)) were predictive of functional dyspepsia.

Conclusion:

This study supported that psychosocial symptoms were related with FD. As most of the patients who had Functional Dyspepsia were married, this could have attributed the significant association between marital status and Functional Dyspepsia.

CHAPTER ONE

INTRODUCTION

1.1 Dyspepsia

Stomach pain and discomfort have been reported since ancient time. The term "dyspepsia" originates from Greek which means indigestion (Brun and Kuo, 2010). It was first recorded in the mid 18th century and since then it has been widely used and also was thought to be one of the "nervous disorders" along with hypochondria and hysteria (Hare, 1991).It is also a common gastrointestinal (GI) complaints worldwide but the definition of dyspepsia has evolved over the past 50 years (Drossman *et al.*, 1993).

Despite numerous international meeting, its definition remains controversial (El Serag and Talley, 2004). This is due to several reasons and among them include an overlap between heartburn and upper abdominal pain and discomfort (El Serag and Talley, 2004).In addition to that, the cultural value also plays an important role as different culture might interpret the pain differently (El Serag and Talley, 2004).

However, the most authoritative definition of dyspepsia based on a consensus meeting of international experts which is also known as Rome committee define dyspepsia as a complex of an upper abdominal symptoms consisting of an upper centred discomfort or pain, feeling of abdominal fullness ,early satiety , bloating and nausea (El Serag and Talley, 2004).

Generally dyspepsia can be divided into:

i. Organic dyspepsia : It has an underlying organic cause such as peptic ulcer

disease, gastric cancer, oesophagitis or other structural abnormalities (Talley, 2005).

ii. Functional dyspepsia : It is a clinical syndrome that has no definite structural or organic cause (Talley, 2005)

Various studies done in Europe , North America and Oceania have shown that the prevalence rates of dyspepsia in between 3% to 40% and these variations of the prevalence rates are due the difference definition used(Shaib and El-Seragh, 2004) The prevalence is lower if patients with any symptoms of heartburn and regurgitation are excluded (Mahadeva and Goh, 2006).

The terms uninvestigated dyspepsia (UD) on the other hand is used to describe dyspepsia that is not being investigated (Mahadeva and Goh, 2006) . The prevalence of uninvestigated dyspepsia varies throughout the world depending on the definition of dyspepsia used in the study (Mahadeva and Goh, 2006). Mahadeva and Goh in their review regarding the prevalence of dyspepsia showed that the prevalence of uninvestigated dyspepsia was 7% to 8% in Singapore, while in Scandinavia it was about 14.5% to 18.4% . It was a bit higher in India and New Zealand in which the prevalence was 30.4% and 34.2% respectively (Mahadeva and Goh, 2006).The prevalence of UD was within the range of 18% to 38% when Rome I criteria was used while it was within the range of 23% to 25% if Rome II criteria was used (Mahadeva and Goh, 2006).

However, in most dyspepsia cases, no visible pathology could be identified from endoscopy as well as no other tests could indicate any underlying organic abnormalities and this condition could be terms as Functional Dyspepsia or non

ulcer dyspepsia (FD) 4,(Welén *et al.*, 2008) .

Functional Dyspepsia can have a great impact on the patients' life. Apart from reducing the patients' quality of life (Halling *et al.*, 2008),it can also lead to increase time off from work(Haycox *et al.*, 1999), frequent clinical consultations (Haycox *et al.*, 1999) as well as increase the cost of treatment (Agreus and Borgquist, 2002; Moayyedi and Mason, 2002).In addition to that, the associated risk factors for Functional Dyspepsia in particular the association with sociodemographic and lifestyle factors remain unclear and are likely to be multifactorial (Zagari *et al.*, 2010). However, previous studies in the past demonstrated its association with psychological factors such as anxiety and depression (Li *et al.*, 2002; Aro *et al.*, 2009).

The most widely applied criteria used in previous studies were the Rome I and Rome II criteria . Due to the strict criteria in Rome II criteria, a new Rome III criteria was introduced by the Rome committee (Drossman and Dumitrascu, 2006b). There were many changes made in Rome III criteria in which there were two subtypes of FD identified namely Epigastric Pain Syndrome (EPS) and also Postprandial Distress Syndrome (PDS) (Drossman and Dumitrascu, 2006b). However, little is known about the existence of this subtypes especially in our Malaysian community.

CHAPTER TWO

LITERATURE REVIEW

2.1 Functional dyspepsia

Functional dyspepsia is defined as the presence of symptoms which is thought to originate from gastroduodenal region, in the absence of any organic,systemic or metabolic disease that is likely to explain the symptoms (Tack *et al.*, 2006).It is one of the recognized Functional Gastro Intestinal Disease (Drossman, 2006b).

It is also referred to as “Dyspepsia Symptom Complex “ and has been categorized into (Tack *et al.*, 2006) :

i. Postprandial Distress Syndrome (PDS) : which include symptoms such as postprandial fullness,early satiety, upper abdominal bloating,postprandial nausea and excessive belching.

ii. Epigastric Pain Syndrome (EPS) : These include symptoms such as epigastric pain which is intermittent , not generalized to other abdominal or chest regions, not relieved by defeacation or passage of flatus and not fulfilling the criteria for gallbladder and sphincter of Oddi disorders. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting (Tack *et al.*, 2006).

2.2 The prevalence of Functional Dyspepsia.

The prevalence of FD in the general population is sparse as it requires endoscopic examination and also due to different criteria used in different studies (El Serag and Talley, 2004; Mahadeva and Goh, 2006). Generally, its prevalence is within the

range of 11% to 29.2% (Mahadeva and Goh, 2006; Zagari *et al.*, 2010).

One study conducted in the United States of America found that the prevalence of functional dyspepsia if the reflux symptoms were included was 29.2% while if reflux symptoms were excluded was 15% (Shaib and El-Seragh, 2004) .This study involved 465 employees with the response rate of 44%, of whom were Caucasians (34.6%), African American (42.8%) as well as other ethnic background (22.6%).

The Norwegian study gave a similar figure in which the prevalence of non ulcer dyspepsia or functional dyspepsia was 14.7% in which 2027 participants were contacted and an 89% response rate was achieved (Bernersen *et al.*, 1996)

A study in Italy using modified Rome II criteria and involving 1533 adults aged 32 to 84 years old with the response rate of 67.4% (n = 1033) found that the prevalence of FD was 11% . It was also found that it was more common among women (9.7% in men versus 12.5% in women) (Zagari *et al.*, 2010).However, no association was found between gender and FD (Zagari *et al.*, 2010).

In Asian region, one study conducted in Taiwan found that the prevalence of functional dyspepsia was 11.8% using Rome II criteria while it was 23.8% if Rome 1 criteria was used (Lu *et al.*, 2005).The difference of the prevalence rate is due to the difference definition used in different criteria(Lu *et al.*, 2005). The study was conducted among Taiwanese population who received paid physical check up with the total of 2865 subjects and the response rate of 70.4% (n = 2018).

While most of the studies conducted earlier used Rome I and Rome II criteria, one study conducted in Sweden which also known as Kalixanda study used the recent Rome III criteria and found that the prevalence of FD was 15.7% involving 1001 subjects who were invited to undergo endoscopy (Aro *et al.*, 2009).

2.3 Social and economic implication

Although FD is non life threatening, it has an important social and economic implication.It causes heavy economic burden due to extensive medical care and diagnostic procedures and also work absenteeism .In one community survey of several European and North American populations, 20% of patients who suffer from dyspepsia consulted the doctors either at primary care clinics or hospitals. In fact more than 50% of them were on medications and 30% of them were reported to be absent from work (Haycox *et al.*, 1999).

This was supported by a study conducted by Pissevaux et al who found that about 36.5% of dyspeptic patient underwent endoscopy while 12.4% of them absent from work or educational activities as a result of their symptoms (Piessevaux *et al.*, 2009).

In primary care setting,Welen et al investigated the Health Related Quality of Life (HRQoL) among patients with FD and the gender differences among patients with FD (Welén *et al.*, 2008).Compared with the control groups they found that HRQoL of patients with FD was impaired in all domain except one role limitations caused by emotional problems(Welén *et al.*, 2008). Female patients were found to have to a significantly lower score in the physical functioning dimension than the male

counterparts with FD(Welén *et al.*, 2008). Both groups of patients had impaired HRQoL as compared to the control group in terms of bodily pain and general health. Women and men with FD were found to have a significant impairment in the dimensions of physical functioning and depression respectively as compared to the control groups (Welén *et al.*, 2008).

Regarding the cost of FD, a Swedish study estimated that the total costs of dyspepsia , peptic ulcer and gastro eosophageal reflux disease in 1997 was US$63 per adult (Agreus and Borgquist, 2002).

While in United Kingdom, a survey on the impact of dyspepsia on quality of life on 5056 patients found that the health service on patients with dyspepsia was costing about £11.25 per person per year, which if representative gives a total cost to the health service of £500 million each year (Moayyedi and Mason, 2002). These include the cost of clinician time, endoscopies as well as the medications(Moayyedi and Mason, 2002) .

Apart from that it was also found that the economic cost of dyspepsia in the community among 8473 participants was £21 per person per year. If this is to represent these population, the total of the cost would be £1 billion each year in the UK. These costs include the time taken off from work as well as the use of over the counter medications. Thus, dyspepsia carries a huge clinical and economic burden to the society (Moayyedi and Mason, 2002)

2.4 Overlapping conditions

Earlier studies found that there were a large overlap between gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS) and FD. A study conducted by Piessevaux et al found that 33.8% of their participants who had FD also had GERD symptoms (Piessevaux *et al.*, 2009).

This is supported by another study conducted among Japanese workers who visited a clinic for a routine health check-up(Kaji *et al.*, 2010). Prevalence and overlap rate of GERD defined as heartburn and/or acid regurgitation at least weekly, FD and IBS based on Rome III criteria, and Health Related Quality of Life (HRQoL) were examined. The results of this study showed that of 2680 participants, 7.7% (207) were diagnosed as having GERD, 10% (269) of them as FD, and 14.2 % (381) as IBS (Kaji *et al.*, 2010). Overlaps were found in 46.9% in GERD, 47.6% in FD, and 34.4% in IBS. Prevalence of overlaps in subjects with IBS was significantly lower compared with those among GERD or FD (Kaji *et al.*, 2010).

These patients (GERD, FD and IBS) had a significant poorer HRQoL across all domains as compared with controls. These overlaps were also found to significantly worsened HRQoL in most domains except in the ‘role emotional’domain. HRQoL was particularly poor in the physical component summary for overlapping GERD and in the mental component summary for overlapping IBS (Kaji *et al.*, 2010).

2.5 Associated factors

There are many studies conducted in order to identify the associated factors for FD. Among the parameters studied were:

2.5.1 Age

Most studies conducted earlier found that age is not predictive of FD. However, a few studies showed some trend in which Uninvestigated Dyspepsia tend to have a peak at the age of 45 to 54 in one of the Canadian study (Tougas *et al.*, 1999) while in Chinese study the peak prevalence of Functional Dyspepsia is at the age of 41 to 50 years old (Li *et al.*, 2002). In Japanese study, lower prevalence of FD was noted among female patients over 70 years of age (Okumura *et al.*, 2010).

2.5.2 Gender

Several studies show that there is a female preponderance with functional dyspepsia.A study conducted in Taiwan found that female gender is an independent risk factor for FD (Lu *et al.*, 2005). Koloski et al also found higher prevalence of functional GI disorders including Functional Dyspepsia in female patients (Koloski *et al.*, 2002) .

Welen et al in their study conducted in Primary Care Clinics found that female patients with FD had a significantly lower HRQoL Short Form 36 Health Survey in the physical functioning dimensions than did the males counterparts (Welén *et al.*, 2008) .

2.5.3 Ethnicity

There are not many studies to look at the role of ethnic background in FD. Uninvestigated Dyspepsia was found to occur more commonly among African American in one of the study conducted in the United States (Shaib and El-Seragh, 2004). In another study conducted by Ho et al in Singapore found that the prevalence of Uninvestigated Dyspepsia was quite similar in all 3 ethnic backgrounds in which it was 8.1%,7.3% and 7.5% for Chinese, Malays as well as Indians respectively (Ho *et al.*, 1998) .However, there was no data found regarding the effect of ethnicity on FD.

2.5.4 Smoking status

Many studies conducted earlier found that smoking is associated with uninvestigated dyspepsia (Tougas *et al.*, 1999; Moayyedi *et al.*, 2000; Shaib and El-Seragh, 2004). However, there is conflicting evidence regarding the association of smoking with Functional Dyspepsia. Anyway, most of the studies found that there was no association observed between smoking status and Functional Dyspepsia (Koloski *et al.*, 2002; Li *et al.*, 2002; Lu *et al.*, 2005).

There was one large population study recently conducted in Italy involving 1533 subjects with the response rate of 67.4% found that smoking seemed to be associated with meal related symptoms or post prandial dyspepsia (OR,1.74;95% CI,1.11-2.70)(Zagari *et al.*, 2010).

2.5.5 Socio-economic associations

There was a strong association noted between lower household income (relative to income >$45,000 per year) and greater reporting frequency for almost all functional gastrointestinal diseases including Functional Dyspepsia in one study conducted by Drossman et al (Drossman *et al.*, 1993).In general, the lower the household income, the greater the symptom reporting (Drossman *et al.*, 1993)This is supported by another study conducted in China in which "dissatisfaction with financial income" was found to be associated with Functional Dyspepsia(Li *et al.*, 2002) .Another population study conducted in Italy found that unemployment and divorce seemed to increase the risk of FD (Zagari *et al.*, 2010).

2.5.7 Psychosocial associations

Most of the population studies found that psychological disturbances as a risk factor for FD. In one study Talley et al found that there was a significant association between sexual abuse, emotional or verbal abuse in childhood and adulthood with dyspepsia as well as visiting the physician for bowel symptoms (Talley *et al.*, 1994).

This was supported by another study conducted by Bernersen et al who found that there was a higher usage of tranquilizer among FD patients as opposed to the Ulcer Dyspepsia patients and this could be due to anxiety or neurotic behaviour that they had (Bernersen *et al.*, 1996).

Apart from that an Australian survey found that adults with FD had a high score on anxiety and depression (Koloski *et al.*, 2002). A similar observations were found in Chinese study in which FD was found to be associated with depression and

anxiety (Li *et al.*, 2002)while in Kalixanda study found that anxiety but not depression was associated with uninvestigated dyspepsia, functional dyspepsia and post prandial distress syndrome but not to epigastric pain syndrome(Aro *et al.*, 2009).

2.6 Pathophysiology

The pathophysiology of FD has been widely investigated and it was poorly understood . There was no single reasons identified and like other functional GI disorders, it could be explained in the context of biopsychosocial model of illness in which symptoms arose from the interaction between abnormal GI physiology and psychosocial factors (Brun and Kuo, 2010). Specific combinations of physiologic, genetic, environmental and psychological factors in a person would affect the person's perception and interpretation of the symptoms (Feldman *et al.*, 2006).

Several studies have addressed the role of **delayed gastric emptying** and functional dyspepsia (Stanghellini *et al.*, 1996; Quartero *et al.*, 1998; Sarnelli *et al.*, 2003a; Lee *et al.*, 2004). However, most of these studies failed to find out the relationship between dyspeptic symptoms and the severity of delayed gastric emptying (Lee *et al.*, 2004). Nevertheless there was one study found that female sex, having severe postprandial distressed symptoms and vomiting were independently associated with a reduced gastric emptying (Stanghellini *et al.*, 1996).

Apart from that, it was also postulated that an **impairment of gastric accommodation to a meal** could be the cause of Functional Dyspepsia . Accommodation is the ability of the stomach to distend appropriately to the size and

timing of a meal (Brun and Kuo, 2010).Several studies found a significant relationship between a defect in postprandial accommodation of the proximal stomach and symptoms of functional dyspepsia such as nausea, bloating as well as pain among FD subjects (Troncon *et al.*, 1994; Gilja *et al.*, 1996; Salet *et al.*, 1998) .One study supported this postulation in which it was found that restoring of gastric accommodation with a fundus-relaxing drug (Sumatriptan)improved early satiety symptoms among FD subjects (Tack *et al.*, 1998) .

Other than that, **visceral hypersensitivity to gastric distension** also plays an important role in FD .One study found that about 34% of FD subjects had hypersensitivity to gastric distension.This hypersensitivity was found to be associated with a higher prevalence of postprandial pain, belching, and weight loss among patients with functional dyspepsia (Tack *et al.*, 2001).

The role of ***Helicobacter Pylori*** in the pathogenesis of FD has been extensively explored and its' role in FD remains to be controversial . Despite one meta analysis on 28 studies found that there was some evidence suggestive of an association between H. Pylori infection and dyspeptic symptoms (Jaakkimainen *et al.*, 1999),the other two studies found no convincing evidence that eradication of *H pylori* could relieve the symptoms of functional dyspepsia (Talley *et al.*, 1999a) and the presence of H Pylori infection was not shown to affect gastric emptying rates for solids and liquids, discomfort sensitivity thresholds as well as meal induced gastric relaxation (Sarnelli *et al.*, 2003b) .However, there was selection bias in the former meta analysis in which most of the studies included were those that showed a positive result and those that were published in English language (Jaakkimainen *et*

al., 1999).

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The role of fat and acid in aggravating the dyspeptic symptoms were also studied. One study found that intraduodenal lipid infusion induced dyspeptic symptoms such as nausea and bloatedness as well as it could increase the sensitivity to gastric distension among the patients with FD (Barbera *et al.*, 1995) .Cholecystokinin(CCK) and 5-hydroxytrptamine (5-HT3)(CCK) receptors played an important role in mediating the effects (Feinle *et al.*, 2001; Tack and Sarnelli, 2002). While other study found that intraduodenal infusion of acid could increase the sensation of nausea among FD patients (Samsom *et al.*, 1999) as well as it could lead to poor fundal relaxation (Schwarz *et al.*, 2001).

It was also postulated that FD patients had an **altered antroduodenojejunal motility**. Previous studies found that patients who had dyspepsia had less motor activity at the antral region(Stanghellini *et al.*, 1992; Camilleri *et al.*, 1998). Despite that, some studies found that the Electrogastrography activity of the stomach was not correlated well with the dyspeptic symptoms (Pfaffenbach *et al.*, 1997) and no positive correlation was found between the symptoms score and the motility score(Wilmer *et al.*, 1998).

The theory that FD is associated with **unsuppressed postprandial phasic contractility in the proximal stomach** has also been widely studied. A gastric barostat on 180 patients with functional dyspepsia and in 53 healthy control subjects by Simren et al found that about 15% of FD subjects had this condition and H pylori infection and severe bloating were strongly associated with this unsuppressed post

prandial phasic contractility (Simren *et al.*, 2003). While another study conducted by Pissevaux et al found that changes in gastric wall tension may be involved in producing symptoms that originates from stomach (Piessevaux *et al.*, 2001).

Another postulation made is about the role of **brain gut axis** which consists of the central, autonomic and enteric nervous system (Smith, 2005).The mechanism regarding the interaction of the brain gut hypotheses involve the transmission of the information by the afferent components of the autonomic nervous system from enteric nervous system receptors to the brain via the vagus and spinal pathways. Within the brain, the incoming information is processed and modified by input from centres involved in affective and cognitive functions. The brain then returns information via the parasympathetic (vagus nerve) and sympathetic efferents which modulate accommodation, motility secretory and immunological functions (Smith, 2005).A defect in efferent vagus activity was observed among subsets of patients with FD as compared to normal control(Holtmann *et al.*, 1998; Silva *et al.*, 2002).This abnormality may play a role in the pathogenesis of the disease in FD patients.

A potential causal link between **psychosocial factors and psychiatric disorders** with functional gastrointestinal disorders (FGID) has been studied extensively.A meta analysis done by Henningsen et al in which 244 studies were included found that there was a significant link between anxiety and depression with medically unexplained diseases such as Non Ulcer Dyspepsia (Functional Dyspepsia), Irritable Bowel Syndrome, Chronic Fatigue Syndrome as well as Fibromyalgia. Although the effect sizes for these association were of moderate magnitude but

were highly significant statistically when compared with healthy persons and controls with medical disorders of known organic pathology(Henningsen *et al.*, 2003).

Studies on the relationship between FD and depression have yielded various results. Koloski et al 2002 found that independent predictors for an Functional Gastrointestinal disorders (FGID) were neuroticism, somatic distress, anxiety, bowel habit disturbance, abdominal pain frequency, and increasing age. However, psychological morbidity did not independently discriminate between consulters and nonconsulters with an FGID. They concluded that the link between FGID and psychological morbidity was modest (Koloski *et al.*, 2002).

In another study conducted by Pajala et al on 400 primary care dyspeptic patients undergoing endoscopy , the risk of having “mental illness” (measured by the General Health Questionnaire mostly identifying anxiety and depression) was 4 times higher in dyspeptic patients compared with the control group. However, there was no significant different found between organic and functional dyspepsia group(Pajala *et al.*, 2005).At 1 year follow up of the same group of patients, it was found that the FD group of patients had more dyspeptic symptoms but there was no difference in mental distress or fear of serious illness. They also found that the reduction of dyspeptic symptoms related to alleviation of psychological symptoms and fear of serious illness was only significant in organic dyspepsia group(Pajala *et al.*, 2006).

A study conducted by Li et al in China found that there was a significantly higher psychological symptoms found among FD patients compared to organic dyspepsia

groups among Chinese population. Apart from that it was also found that FD groups of patients had a higher rates of anxiety and depression (Li *et al.*, 2002).

A large population study conducted by Aro et al in 2009 in Kalixanda, Sweden involving 1001 participants found that anxiety was a significant and independent predictor of uninvestigated and functional dyspepsia, whereas depression was not. In addition to that anxiety was found to be associated with Post Prandial Distress Syndrome but not to Epigastric Pain Syndrome (Aro *et al.*, 2009).

It has been postulated that stress can alter gastrointestinal motility , reduce visceral pain threshold and supress the vagal autonomic function leading to an impairment in gastric accommodation and antral hypomotility (Feldman *et al.*, 2006).

Apart from that, patients with both underlying abnormalities in GI physiology and psychological problems, increased life stress or poor social support may be more likely to seek medical attention (Feldman *et al.*, 2006).

2.7 Rome Criteria

There have been many attempts to define Functional Gastrointestinal Diseases (FGID) condition . Manning criteria was developed to define IBS while Collin-Jones criteria was developed to define FD .Later, in 1989 Rome Foundation was formed and Rome 1 Criteria then was developed. Rome was named after the place where they first met. There were more and more research done at the same time that provide evidence that FGID was a brain gut disorder(Drossman and

Dumitrascu, 2006a).

In 1999, Rome II Criteria was developed in order to improve the criteria for Rome I (Drossman, 1999). Rome III then was developed in 2006 with some changes made in Rome II criteria (Drossman and Dumitrascu, 2006a).

2.7.1 Rome I

The Multinational Working Teams developed Diagnostic Criteria for Functional Gastrointestinal Disorders in mid 1980s and published the developed consensus criteria for over 20 FGIDs. These documents were eventually updated and compiled into a book and was named as Rome criteria (Drossman *et al.*, 1994) . The criteria for Rome I is as shown in the Appendix 1.

2.7.2 Rome II

After the development of Rome 1 criteria, many researches found the existence of two distinct subgroups of dyspepsia namely:

i. Ulcer - like dyspepsia where pain is the most predominant symptom.

ii. Dysmotility - like dyspepsia where discomfort and not pain is the most predominant symptom (Talley *et al.*, 1999b).

In addition to that, there is an agreement that symptoms should have run a chronic course before a patient is labelled as having functional dyspepsia (Drossman, 1999). It is therefore recommended that in order to make a diagnosis of functional gastrointestinal diseases, symptoms should be present for at least 12 weeks out of the previous year.

The 12-week qualification is a change from the Rome I criteria, which only require the symptoms to be present in the previous three months. The reasons for this change are that FGIDs are conditions that have a waxing and waning course, and (particularly for epidemiological surveys) symptoms might not have been present in the previous three months, but may have existed prior to that time. The 12 weeks need not be consecutive, and within each week, symptoms are only required for 1/7 days (Drossman, 1999).

The Rome Committee also found that it is essential to perform an upper endoscopy in order to exclude structural abnormalities. However, ultra sonographic examination is not recommended as in outpatients studies most patients have no detectable abnormality in the absence of symptoms or biochemical tests suggestive of biliary tract or pancreatic disease as opposed to the criteria that has been set in the Rome I .(Talley *et al.*, 1999b).In addition to that, a subclassification has been made on predominant symptoms eg.ulcer like dyspepsia , dysmotility like dyspepsia and unspecified dyspepsia (Talley *et al.*, 1999b). The criteria for Rome II were as shown in Appendix 2.

2.7.3 Rome III

There has been a lot of criticism in Rome II criteria because of the difficulty distinguishing pain from discomfort as proposed in Rome II as well as the lack of an accepted definition of the predominant symptoms .In addition to that, there were number of patients who did not fit into one of the subgroups and thus leading to the development of Rome III criteria.

The Rome III criteria for Functional Dyspepsia include:

For the last 3 months at least 1 day per week one or more of the following (Drossman and Dumitrascu, 2006a; Tack *et al.*, 2006):

1.Bothersome postprandial fullness

2.Early satiation,

3. Epigastric Pain

4. Epigastric burning

AND

Onset more than 6 months prior to diagnosis and no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

In addition to these criteria a subclassification has been made.

A. Post Prandial Distress Syndrome (PDS)– defined as bothersome post prandial fullness, occurring after ordinary sized meals, at least several times per week AND/OR early satiety that prevents finishing a regular meal, at least several times per week.

B. Epigastric Pain Syndrome (EPS) which must include all the following : Pain or burning of at least moderate severity , in middle of abdomen at least 1 day per week, pain or burning often disappears completely in the same day, chest pain occurs once a month or less often , never or rarely gets better after defaecation , not fulfilling criteria for gallbladder and sphincter of Oddi disorders.

:2.8 .Main changes in Rome III criteria

There are several changes made in Rome III criteria . These changes are made based on a few reasons that are (Tack *et al.*, 2006):

1.There tend to be an overlapping between Functional Dyspepsia and Gastro Esophageal Reflux Syndrome (GERD). Heartburn does not exclude a diagnosis of FD (PDS or EPS) if dyspepsia persists despite a trial of adequate acid suppression.

2. Overlapping with IBS symptoms – there is also an overlapping with the IBS symptoms.

3. There is no single symptoms present in FD and there is a considerable variation in symptoms patterns between patients.

4.Despite Rome II recommendations, there were a few studies still included heartburn and acid regurgitation as “dyspepsia”.

Based on the above reasons the new Rome III Criteria has been revised and FD is also called Dyspepsia Complex Syndrome and it is an umbrella for Postprandial Distressed Syndrome and Epigastric Pain Syndrome (Tack *et al.*, 2006) .The comparisons between Rome II and Rome III criteria are as shown in the table 1.

Table 1 Comparisons between Rome II and Rome III criteria of Functional Dyspepsia (www.romecriteria.org)

Rome III	Rome II
For the last 3 months at least 1 day per week one or more of the following: 1.Bothersome postprandial fullness 2.Early satiation, 3. Epigastric Pain 4. Epigastric burning AND Onset more than 6 months of diagnosis. No evidence of structural disease from endoscopic findings. In addition to these criteria a subclassification has been made. **A. Post Prandial Distress Syndrome (PDS)** bothersome post prandial fullness, occurring after ordinary sized meals, at least several times per week AND/OR early satiety that prevents finishing a regular meal, at least several times per week. **B. Epigastric Pain Syndrome (EPS)** which must include all the following : Pain or burning of at least moderate severity , in middle of abdomen at least 1 day per week, pain or burning often disappears completely in the same day, chest pain occurs once a month or less often, never or rarely gets better after defaecation, not fulfilling criteriafor gallbladder and sphincter of Oddi disorders.	The presence of these symptoms in at least 12 weeks which need not be consecutive in the preceeding 12 months of: 1.Persistent or recurrent pain or discomfort centred in the upper abdomen(above navel) and 2. No evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms. 3. No evidence that dyspepsia is exclusively relieved by defaecation or associated with the onset of a change in stool frequency or stool form. In addition to these criteria, subclassification has been made **A. Ulcer like Dyspepsia:** Pain centered in the upper abdomen is the predominant symptom. **B. Dysmotility like dyspepsia:** An unpleasant or non painful sensation (discomfort) centered in the upper part of the abdomen ;this sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating or nausea **C. Unspecified or nonspecific dyspepsia:** Symptoms that does not fulfill the criteria for ulcer like dyspepsia or dysmotility like dyspepsia.

2.9 Overview of Rome III Questionnaire

This questionnaire was developed based on Rome III citeria (www.romecriteria.org). It also includes alarms symptoms to alert the physician of possible organic/structural disorders that might require further investigations. It has coding system that identifies provisional (or possible) diagnosis from the response to the questions(www.romecriteria.org).

The alarm symptoms or "red flags" symptoms are also included in the questionnaire. The presence of alarm symptoms such as malaena, haematemesis, loss of weight, history of gastric cancer are potentially indicative of organic diseases that warrant further investigations and necessitates for further evaluation(www.romecriteria.org) .

This questionnaire was developed based on Rome III Criteria and was validated(Drossman and www.romecriteria.org) The estimated specificity for FD , PDS and EPS were 94.1%, 99.3% and 100% respectively. While for Test-Retest agreement for FD, PDS and EPS were 84.6%,85.6% and 98.1% respectively (Drossman and www.romecriteria.org).

In addition to that the psychosocial alarm questionnaires which help to identify any associated psychosocial problems have also been included.This psychosocial alarm component might help the physician to identify the psychosocial problem related to FGID (www.romecriteria.org). Malay language version on IBS and psychological alarm questions based on Rome III criteria

was validated by Lee and Anuar (Lee and Anuar, 2008) . In this study they found that it has a good clinometric properties to serve as a tool for research.

It has a Cronbach's alpha of 0.792 and reproducibility of 0.788 with a lower bound of 0.704 and upper bound of 0.858 (Lee and Anuar, 2008).

2.9.1 Functional Dyspepsia module questionnaire

Funtional Dyspepsia module questionnaire consists of 18 questions (www.romecriteria.org). These questionnaire was developed based on the latest Rome III criteria. The Rome III criteria for Functional Dyspepsia include :

The presence of one or more of :

a. Bothersome postprandial fullness which is the feeling of uncomfortably full after regular sized meal (www.romecriteria.org). It should occur more than 1 day per week(www.romecriteria.org). This is asked in question 3.

In order to fulfill the criteria for Functional Dyspepsia, the score for question number three should be more than "4 "which is *more than 1 day per week* (www.romecriteria.org). In addition to that, the onset of the pain should be more than 6 months ago as in question number 4. The score for this question should be equal to "1" which is it should occur more than 6 months duration (www.romecriteria.org).

b. Early satiation means inability to finish regular sized meal of more than 1 day per week (www.romecriteria.org). This is asked in question number 5 and